REMARKS

The allowability of claim 47-48 is acknowledged. The claims were objected to as being dependent upon a rejected claim. The claims were amended to put them into independent format.

Claims 16, 42-44, and 46-57 are pending. Claims 17-22, 40-41, and 45 were canceled. Claims 16, 39, 42-44, and 46-50 were amended. Claim 16 was amended to incorporate the limitations of originally-filed (and canceled) claims 17-19 and 45. The amendment to claim 39 is supported by disclosure at page17, lines 18-22, of the specification. Claims 46, 49 and 50 were amended to correct dependency.

The specification has been amended to clarify that HAAH polypeptide refers to the amino acid sequence of SEQ ID NO:2 and HAAH cDNA refers to the nucleotide sequence of SEQ ID NO3. The claims have also been amended accordingly. The specification has also been amended to insert a reference to a sequence (SEQ ID NO:2) on page 6, line 16.

With respect to the Declaration/ Power of Attorney, co-inventor, Dr. Carlson, has initialed and dated the correction of his home address. An initialed/dated copy of the Combined Declaration and Power of Attorney document is submitted herewith.

No new matter has been added by this amendment.

35 U.S.C. § 112, second paragraph

Claims 16-22, 39-44, and 49-56 were rejected for indefiniteness for recitation of "HAAH" as the only means of identifying a protein to which the claimed antibodies bind. As requested by the examiner, the claims have been amended to insert a sequence identifier.

35 U.S.C. § 112, first paragraph

Claims 42 and 43 were rejected for lack of enablement. The claims have been amended to identify an antibody-producing hybridoma cell line, which was deposited with the ATCC. A copy of the ATCC deposit receipt is submitted herewith.

Claims 16, 17, 39, 40, 41, and 49-56 were rejected for overbreadth. In item 11 (page 7) of Paper No. 10, the Examiner stated that the claims were rejected

> because the specification, while being enabling for a method of inhibiting tumor growth in a mammal comprising the administration of an antibody conjugated to a chemotherapeutic agent or an antibody capable of eliciting antibody dependent cytotoxicity (ADCC) or complement dependent (CDCC), does not reasonably provide enablement for a method of inhibiting tumor growth in a mammal comprising administration of an antibody or an intrabody which binds to the intracellular domain of HAAH.

Claims 17, 40, and 41 were canceled. Claim 16 was amended to require a dominant negative mutant of HAAH (and is, therefore, no longer drawn to an antibody). Claim 39 was amended to require an antibody linked to a cytotoxic agent. In view of these amendments, Applicants request withdrawal of this rejection.

Claims 16, 17, 52, 55, and 56 were rejected for lack of enablement. The Examiner stated that "while being enabling for a method of treating non-central nervous system tumors by means of an antisense construct to HAAH, does not reasonably provide enablement for a method of treating a central nervous system tumor". None of the amended claims require antisense compositions. Therefore, this rejection should be withdrawn.

Claims 16-22, 39-44, and 49-56 were rejected for written description. In item 13 (page 12, lines 11-14 of Paper No. 10), the Examiner stated:

> According to these facts one of skill in the art would conclude that the applicant was not in possession of the claimed genus because a description of only one member of this genus, SEQ ID NO:2, is not representative of the variants of the genus and is therefore insufficient to support the claims.

The claims have been amended to insert a sequence identifier for SEQ ID NO:2. Therefore, this rejection can now be withdrawn.

35 U.S.C. § 102

Claims 16, 17, and 21 were rejected for anticipation by De Wys et al. (as evidenced by Hanauske-Abel). De Wys et al. was cited for a description of mimosine. Claims 17 and 21 (which recited L-mimosine) were canceled, and claim 16 was amended to require an HAAH polypeptide with a mutation in a catalytic domain, which is defined by residues 650-700 of SEQ ID NO:2. DeWys et al. fail to describe the HAAH mutant now required by the claims.

Claims 16, 17, and 22 were rejected for anticipation by Fujii. Fujii was cited for a description of hydroxypyridone. Claims 17 and 22 (which recited hydroxypyridone) were canceled. The HAAH mutants now required by the claims are neither described nor suggested by this reference.

In view of the present amendment, Applicants request withdrawal of this rejection.

35 U.S.C. § 103

The claims were rejected for obviousness over several combinations of references, each of which is addressed below.

Ullrich et al. in view of Jia et al., Korioth et al., and Lavaissiere et al.

Claims 16, 17-19, and 44-46 were rejected for obviousness over Ullrich et al. in view of Jia et al., Korioth et al., and Lavaissiere et al. Claims 17-19 and 44-45 were canceled, the limitations thereof being incorporated into amended claim 16.

On page 22, lines 1-8 of Paper No. 10, the Examiner states:

> It would have been *prima facie* obvious to one or ordinary skill in the art at the time the claimed invention was made to make a dominant negative mutatnt of HAAH by substitution the his-675 residue with alanine, and adminster said mutant to a mammal to inhibit tumor growth. One of ordinary skill in the art would have been motivated to do so with reasonable expectation of success by the teachings of Jia and Korith on the necessity for the His-675 residue for hydroxylation activity in HAAH and the suggestion of Lavaissiere et al. on the need to establish the associative or causal nature of the increased hydroxylation activity by HAAH in carcinoma cells.

The cited combination of references fails to establish *a prima facie* case for obviousness. The examiner states that the primary reference, Ullrich et al., describes a dominant negative mutant of VEGF. Rather, Ullrich et al. describe dominant negative mutants of Flk-1, a VEGF receptor, i.e., truncated forms of the receptor lacking most of the cytoplasmic domain of the receptor. Secondary references, Lavaissiere et al., Jia et al., and Korith et al. describe aspartyl (asparaginyl) beta hydroxylases. The VEGF receptor, Flk-1, and aspartyl (asparaginyl) beta hydroxylase are completely different proteins that differ significantly in both structure and function. There is no suggestion in either Ullrich et al. or any of the secondary references that these two classes of proteins have anything in common.

None of the secondary references describe or suggest mutating HAAH in any way. Thus, there is no suggestion or motivation to make a dominant negative mutant of HAAH, much less a mutant containing a mutation in a specific region, residues 650-700 of SEQ ID NO:2, as claimed.

Moreover, even if the references were properly combined, none of the references describe or suggest the specific limitations of the amended claims. The claims require a mutation in the catalytic domain, the domain being defined by residues 650-700 of SEQ ID NO:2. For example, the Examiner states:

> One can conclude by this comparison [Jia et al. and Korioth et al.] that the his-2 motif in human HAAH includes the same residues and thus the catalytic domain consists of residues 675-692 of human HAAH.

However, the specification teaches (and the claims require) that the catalytic domain is defined by residues 650-700 of SEQ ID NO:2 (HAAH). In fact, the specification teaches that conserved residues of the catalytic domain are residues 660-663 and 670-673 (Table 2, page 5, of the specification), which residues are outside of the boundaries allegedly suggested by the combined teachings of the references.

Applicants therefore submit that a *prima facie* case of obviousness has not been established and respectfully request withdrawal of this rejection.

Dietz in view of Radosevich

Claims 16, 17, 51, and 52 were rejected for obviousness over Dietz in view of Radosevich. In item 20 (page 19, lines 15-17), the Examiner stated:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer the antisense nucleic acid of Radosevich to a mammal having hepatocellular carcinoma.

Neither originally-filed claims 16, 17, 51, and 52 (nor the amended claims) require an antisense nucleic acid. Therefore, this rejection should be withdrawn.

Schlom in view of Lavaissiere et al.

Claims 16, 17, 39, 41-43, 51 and 53 were rejected for obviousness over of Schlom in view of Lavaissiere et al. Independent claim 16 was amended to require a dominant negative mutant of HAAH characterized by a mutation in a catalytic domain defined by residues 650-700 of SEQ ID NO:2. Neither Schlom nor Lavaissiere et al. describe or suggest a dominant negative mutant of HAAH, nor do they suggest the domain now required by the claims.

In view of this amendment, withdrawal of this rejection is respectfully requested.

Schlom in view of Sinkule et al and Radosevich

Claims 16, 17, 39, and 41 were rejected for obviousness in view of Schlom in view of Sinkule et al and Radosevich. As is discussed above, claim 16 was amended to require a dominant negative mutant of HAAH defined by a mutation located within residues 650-700 of SEQ ID NO:2. No such composition is described or suggested by this combination of references. Therefore, the amended claims are nonobvious over Schlom in view of Sinkule et al and Radosevich.

Conclusion

Based on the foregoing, this application is believed to be in allowable condition, and a notice to that effect is respectfully requested. The Examiner is invited to call the Applicants' Attorney at the number provided below with any questions.

Applicants file concurrently herewith a petition for a two (3) month extension of time, together with a check for $930.00 to cover the fee pursuant to 37 C.F.R. § 1.17(a)(3). With the extension, this amendment is due on or before July 15, 2003. The Commissioner is hereby authorized to charge same, or credit any overpayment, to Deposit Account No. 50-0311 (Reference No. 21486-032 DIV2).

Respectfully submitted,

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